Delayed Reaction: The Fetal Basis of Adult Disease, with Deborah Cory-Slechta

Ashley Ahearn

Exposure to certain chemicals or stressors *in utero* can cause immediate health effects for fetuses and babies including lowered birth weight, birth defects, and impaired neurodevelopment. New lines of research are now showing that prenatal exposures may also contribute to health problems that typically arise later in life—such as obesity, diabetes, cardiovascular disease, cancer, and Parkinson disease—via changes to DNA transcription and the hypothalamic–pituitary–adrenal axis. In this podcast, Deborah Cory-Slechta discusses the phenomenon known as the fetal basis of adult disease. Cory-Slechta is a professor of environmental medicine at the University of Rochester School of Medicine and Dentistry.

AHEARN: It's *The Researcher's Perspective*. I'm Ashley Ahearn.

When we are exposed to certain chemicals or stressors in the womb, research has shown there are certain immediate health problems that may arise—lowered birth weight, birth defects, or impaired neurodevelopment, to name a few.

But what about health problems that typically arise later in life—obesity, cardiovascular disease, cancer, Parkinson's disease? Could these also be the result of exposure to certain substances early in our development?

More and more research is being done to explore what's called the "fetal basis of adult disease hypothesis."

Joining me to talk about it is Dr. Deborah Cory-Slechta. She's a professor of environmental medicine at the University of Rochester School of Medicine and Dentistry.

Dr. Cory-Slechta, thanks for being here.

CORY-SLECHTA: Glad to be with you.

AHEARN: Let's start by laying out this hypothesis, the fetal basis of adult disease. What is it?

CORY-SLECHTA: Well, it actually started with some work done by Dr. Barker[1] back many years ago looking at victims of a Dutch famine. And what he saw in those individuals was that those who suffered under-nutrition in the womb later in life had a much higher incidence of a variety of different diseases and disorders, particularly cardiovascular disease, hypertension. There were also cognitive kinds of problems, a real assortment of different diseases, and that's what really got this whole area of the fetal basis of adult disease off and running, so to speak—that you could have something going on early in life, this under-nutrition, and even if those children ultimately caught up nutrition-wise with children who didn't have early under-nutrition, they still ended up having this higher episode incidence of diseases and disorders later in life.

AHEARN: But this hypothesis now stretches beyond just under-nutrition in terms of stressors. We're looking at exposures as well, right?

CORY-SLECHTA: We're looking at, actually, a variety of different things. Yes, it does expand beyond that. So one of the things that's become clear is that early under-nutrition itself can cause a variety of diseases and disorders later in life, and there are multiple ways in which that seems to happen. One is through something called epigenetics where you have an influence on what's called the transcription of DNA—not a change in the DNA itself, the structure of the DNA, but in how it gets transcribed or activated. You can have what appear to be permanent changes in something called the HPA axis, the hypothalamic–pituitary–adrenal axis. That's the body's system that controls responses to stress, and when you have early or maternal prenatal stress you can cause increases in stress hormones in the fetus that basically result in permanent changes in the HPA axis. That HPA axis change can lead, itself, to many different diseases and disorders because it controls a lot of those organ systems.

Also, now we're beginning to look at a lot of environmental exposures that probably through these different mechanisms, like epigenetics or changing the HPA axis, among others, thereby lead to these diseases and disorders by permanently changing these mechanisms.

AHEARN: What other diseases that manifest later in life do you think could be tied to early developmental exposures?

CORY-SLECHTA: Well, let me use lead exposure as an example of that, something we know a lot about. We know that lead exposure early in life is one of the kinds of exposures that can permanently change this HPA axis function. Lead exposure early in life has been tied to later hypertension, cardiovascular disease, diabetes, schizophrenia, neurodegenerative changes, all of which may occur through these changes in the HPA axis function. That's just one example. We haven't studied a lot of these other chemicals, but I think we're going to be seeing some similar kinds of things. Other examples are endocrine disruptors, things like bisphenol A or phthalates, which affect sex steroid hormones. Those two are producing permanent changes early in development, in this case in hormonal systems that basically target lots of different organs in the body. So it's really going to be a variety of different diseases and disorders that are ultimately, I think, going to get tied back to some of these kinds of exposures.

AHEARN: Why does it take so long? When you're looking at a disease that can crop up 65 years later, 70 years later, what's going on in the interim?

CORY-SLECHTA: Things like epigenetics really can explain that because you're producing changes in essentially the transcription or activation of a gene that can be lifelong kinds of changes. If they occur in the sperm or the egg, they can actually then be transmitted to the next generation so now we have the possibility not only of you having these epigenetic changes that can manifest themselves in diseases and disorders later in life, but that you could transmit to your offspring. When you change things like the HPA

axis early in life it can be thought of like a thermostat that you've now reset and you can't change it back again. So it never operates correctly later in life either. The brain development has to unfold; a sequence of steps has to unfold perfectly in time. If you change that early in life, then it's broken. It never can refix itself because the time at which it goes through development has long since passed. So there's really no way to repair some of these changes. They're basically now set in stone for life.

And I think partly the other really important thing about this whole field of fetal basis is that those effects are extremely gender-specific.

AHEARN: Could you talk a little bit more about those gender differences? I mean, am I more vulnerable as a baby boy than a baby girl?

CORY-SLECHTA: Well, it depends on the disease that we're talking about. So if you think about something like Parkinson's disease we know that it has a higher prevalence in males; that is, females are protected against this disease. One of the thoughts about that is that it relates to estrogen somehow, and estrogen, of course, is something that if you modify that early in life during the differentiation of the brain, you can have permanent kinds of consequences. Or if you modify testosterone early in life, you can have permanent consequences.

If we're talking about schizophrenia, there's not so much of a different incidence or prevalence in males and females, but the schizophrenic syndrome manifests very differently by gender. If you think about things like attention deficit/hyperactivity disorder, again, something that we really don't understand in terms of its etiology, it has a higher prevalence in boys than girls, whereas Alzheimer's disease has a higher prevalence in women than in men; at least, most studies would say that. So you see these very, very clear gender differences, and these are things that are very likely to translate back into epigenetic changes that differ [between males and females], changes in HPA axis programming, which are different in males versus females, or hormonal changes that occur very early in life.

AHEARN: Dr. Cory-Slechta, what's to be done with this growing body of research we have on the fetal basis of adult disease?

CORY-SLECHTA: Well, let me take it a couple directions. One, I think it will tell us a lot about what we need to do better maternal health, maternal screening, in terms of preventing these kinds of effects that might lead to later diseases and disorders in children. With respect to experimental exposures, we really haven't had the data to be able to incorporate this kind of information into risk assessment paradigms. Once it comes there will really be policy issues about how we're going to deal with this kind of information. What would it mean with respect to exposure levels that are safe? How much would it cost to decrease those kinds of exposures? So it can have a lot of those sorts of implications above and beyond the scientific data that comes out of these studies.

AHEARN: What makes *you* want to study the fetal basis of adult disease?

CORY-SLECHTA: Well, it's a really interesting area because it's this connection between something that happens early on and something later in life. I hope it's, as I said before, going to really allow us to understand how environmental chemicals influence health or lead to diseases and disorders. I think without that understanding we may be underestimating the risks that are actually posed by environmental chemicals, because we don't understand or we aren't aware at this point of whether they are having these kinds of influences. I think it's a really exciting area of research. It may hold a lot of answers to things that have eluded us for a long time.

AHEARN: So you're in this for the long haul.

CORY-SLECHTA: Oh yeah, I think it's a great area of research. It just has a lot of promise for better understanding of human diseases and disorders, and that's why you're in this field to begin with.

AHEARN: Dr. Cory-Slechta, thanks so much for joining me.

CORY-SLECHTA: Thank you, Ashley. Nice to be here.

AHEARN: Dr. Deborah Cory-Slechta is a professor of environmental medicine at the University of Rochester School of Medicine and Dentistry.

And that's *The Researcher's Perspective*. I'm Ashley Ahearn. Thanks for downloading!

Note

1. David J.P. Barker first reported an association between impaired fetal growth and chronic disease later in life in the seminal article "Infant Mortality, Childhood Nutrition, and Ischaemic Heart Disease in England and Wales" [Lancet 327(8489):1077–1081 (1986)]. Barker's hypothesis is sometimes called the thrifty phenotype hypothesis.

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